

Effects of Ephedrine, Caffeine, and Their Combination on Muscular Endurance

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ABSTRACT

JACOBS, I., H. PASTERNAK, and D. G. BELL. Effects of Ephedrine, Caffeine, and Their Combination on Muscular Endurance. *Med. Sci. Sports Exerc.*, Vol. 35, No. 6, pp. 987-994, 2003. **Purpose:** The purpose of this study was to investigate the effects of ingesting caffeine (C), ephedrine (E), and their combination on muscular endurance, using a double-blind, repeated measures design. **Methods:** Ninety minutes after ingesting either C (4 mg kg⁻¹), E (0.8 mg kg⁻¹), a combination of C+E, or a placebo (P), 13 male subjects performed a weight-training circuit consisting of three supersets (SS), each SS consisting of leg press (at 80% of 1 RM to exhaustion) followed by bench press (at 70% 1-RM to exhaustion), 2 min of rest intervened between SS. **Results:** The trials involving ephedrine ingestion (C+E and E), when compared with the nonephedrine trials (C and P), caused significant increases ($P < 0.05$) in the mean number of repetitions completed for both the leg-press and bench-press exercises but only during the first SS. During that first set, the mean number ($\pm$ SD) of repetitions for leg press was 19 ± 8 , 16 ± 7 , 14 ± 6 , and 13 ± 5 for the C+E, E, C, and P trials, respectively. The mean numbers of repetitions for the first set of bench-press exercise were 14 ± 3 , 13 ± 3 , 12 ± 3 , and 12 ± 3 for the C+E, E, C, and P trials, respectively. As a result, the total weight lifted during all three sets was greater for the trials involving ephedrine ingestion. Systolic blood pressure before exercise was significantly increased with both ephedrine treatment trials when compared with the other trials (C+E = 156 ± 29 mm Hg, E = 150 ± 14 , C = 141 ± 16 , P = 138 ± 14). **Conclusion:** It was concluded that acute ingestion of C+E and E increases muscular endurance during the first set of traditional resistance-training exercise. The performance enhancement was attributed primarily to the effects of E, there was no additive effect of C. **Key Words:** ERGOGENIC AIDS, HUMAN PERFORMANCE, STIMULANTS, DOPING, RESISTANCE TRAINING

Our interest in improving physical performance does not stem from sports but rather with the enhancement of performance that may provide an advantage to military personnel during operations that require intense physical exertion. It is within this context that we have been systematically clarifying the effects of caffeine and ephedrine on physical performance across a broad range of exercise intensities (6-9,12).

It is recognized that the desire to excel in sports can induce athletes to engage in strategies that are unethical and therefore banned by sport regulatory bodies. Such strategies frequently involve the use of nutritional or pharmacological treatments to acutely enhance performance, and their use is therefore considered as cheating within the context of competitive sports. Cheating in sports is not a concern for the population with whom we work, but we are, of course, concerned with health risks associated with performance-enhancing strategies. There is some evidence that the ingestion

of such supplements poses unacceptable health risks (18), but other research suggests that the empirical evidence of such risks does not support such a conclusion (19,26). At the time this research was carried out, both caffeine and ephedrine were unregulated and could be purchased "over-the-counter" without a prescription both in the United States and in Canada. The regulatory status of ephedrine-containing products has been in flux in North America over the last few years, but there is no doubt that ephedrine or ephedra-containing products have been used by a very large number of consumers for the specific purpose of enhancing their physical performance, either competitively or during training. The motivation for such consumption is likely related to the perception that performance is in fact improved, but until recently there has been little supporting empirical evidence.

To be best positioned to provide sound empirically based advice to those who seek our guidance, we thought it appropriate to carry out prospectively designed research into both the performance effects and health risks associated with the acute use of caffeine and ephedrine. The research reported here is one in a series of studies targeting performance effects.

The effects of caffeine (C), ephedrine (E), and their combination on resting metabolic rate have been studied extensively as a chronic treatment for obesity (3-5,13,26). The potential benefit of combining C and E (C+E) is based on the speculation that C induces a "permissive" action on E, both lowering the threshold concentration required for

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physiological effects and potentiating the physiological effects of a given concentration of E (4). It is this mechanism that led to speculation that C+E would also enhance exercise performance, and, as described below, a related series of studies has already documented ergogenic effects associated with the acute ingestion of C+E.

Time to exhaustion during a standard high-intensity cycle-ergometer exercise test was reported to increase from 12.6 ± 3.2 min during the placebo (P) trial to 17.5 ± 5.8 during the C+E trial after ingestion of $1 \text{ mg kg}^{-1} \text{ E} + 5 \text{ mg kg}^{-1} \text{ C}$ (9). This relative improvement in time to exhaustion while exercising at about 85% of maximal aerobic power was extended from an improvement of about 38% to an improvement of 64% by reducing the E and C doses somewhat (8). The time to complete a standard 3.2-km military cross-country march/run while carrying about 11 kg was slightly, but significantly, improved (from 15.4 to 14.7 min) after ingesting a standard dose of $75 \text{ mg E} + 375 \text{ mg C}$ (6). Indices of the capacity to transduce energy into mechanical work via anaerobic metabolism, as well as the peak power generated during a test of anaerobic power, were slightly but significantly improved after ingestion of C+E (7). Time to complete a 10-km treadmill run and the pace throughout the run were measured in subjects who were wearing military light fighting order weighing about 11 kg. After ingesting either $0.8 \text{ mg kg}^{-1} \text{ E}$ or the E combined with $4.0 \text{ mg kg}^{-1} \text{ C}$, run times were about one min faster when compared with the P trial time of 46.8 ± 3.2 min, primarily due to a faster pace over the last 5 km of the run (12).

Taken together, the available literature is interpreted as indicating that C+E has very potent acute ergogenic characteristics. The magnitude of the performance improvements varies substantially depending on the intensity of exertion. No studies have been published about the effects of C+E on the kind of exercise used during traditional resistance training. Bell et al. (7) speculated that the likely primary mechanism of action explaining physical performance enhancement after the ingestion of C+E is the stimulation of the CNS, mediated by adenosine receptor antagonism. This hypothesis is supported by the report that C+E ingestion causes a decrease in the rate of perceived exertion (RPE) during high-intensity exhaustive exercise (8). We speculated that such increased CNS stimulation would likely also affect muscular endurance and strength. This study was designed to test the hypothesis that ingestion of C+E would enhance muscular endurance and that the magnitude of the effect would be greater when compared with trials where C or E is ingested alone. Standard strength training exercise regimes offer a test paradigm that is very familiar to subjects accustomed to resistance training. For this reason, the performance test investigated in the current investigation was designed to be akin to the kind of training that subjects might employ in the course of routine recreational strength training.

METHODS

Subjects. When designing this research project, an *a priori* analysis was performed with a view to having a sufficient number of subjects for a statistical power of 0.8 based on an expected treatment effect that would cause a 30% difference in the number of repetitions performed in one set of exercise. This magnitude of change was chosen because of literature reporting similar relative increases in muscular endurance after about 6 wk of training (2,24). It was felt that if a similar performance enhancement was evident within only 2 h after drug ingestion, then it was highly significant from a functional perspective. This analysis indicated that a sample size of 12 subjects would be appropriate. Allowing for the possibility of subject attrition during the experiment, we recruited 13 volunteers.

The protocol was approved by institutional research ethics boards at the Defence & Civil Institute of Environmental Medicine and at the University of Toronto. Written informed consent was obtained from all subjects before beginning data collection. The research complies with the *Medicine & Science in Sports & Exercise*, "Policy Statement Regarding the Use of Human Subjects and Informed Consent."

The subjects were healthy, active male subjects 18–34 yr of age, with a mean ($\pm$ SD) weight of 72 ± 11 kg and height of 176 ± 8 cm. None of the subjects was training as a competitive athlete, but all subjects engaged in recreational fitness training. A criterion for participation was that the subject was experienced with resistance training exercises and was either currently engaged in resistance training or had done so within the preceding year. It was decided *a priori* not to include female subjects because the effects of a combination of caffeine and ephedrine on a fetus are unknown, and it was felt that the inadvertent exposure of a fetus to these drugs constituted an unacceptable and avoidable risk. Normal dietary caffeine intake in the subjects was neither controlled nor measured other than to identify that none of the subjects avoided caffeine ingestion. For the dosage of caffeine used in this investigation, caffeine half-life has been reported to range from 2.5 to 4.5 h (16). To permit a sufficient interval for caffeine "washout," subjects were informed that they had to abstain from consuming coffee for 48 h before each trial as well as alcohol and any medication. They were also instructed to maintain their normal exercise regime but to avoid any hard exercise for 24 h before each visit.

Procedures. Subjects reported to the laboratory on nine different occasions. During the initial visit, a physical examination and medical history were conducted by a physician to ensure that they were fit to participate in the experiment. Their one-repetition maximum (1-RM), i.e., the maximum weight that could be lifted once, was estimated for the legs and the arms (27). The leg-press exercise was performed in a supine position (Fig. 1) on a plate-loaded 45° angle leg-press apparatus (ASC-101, Atlantis, Canada). The arm bench press (Fig. 2) was performed on a bench-press apparatus (ASE-155, Atlantis).

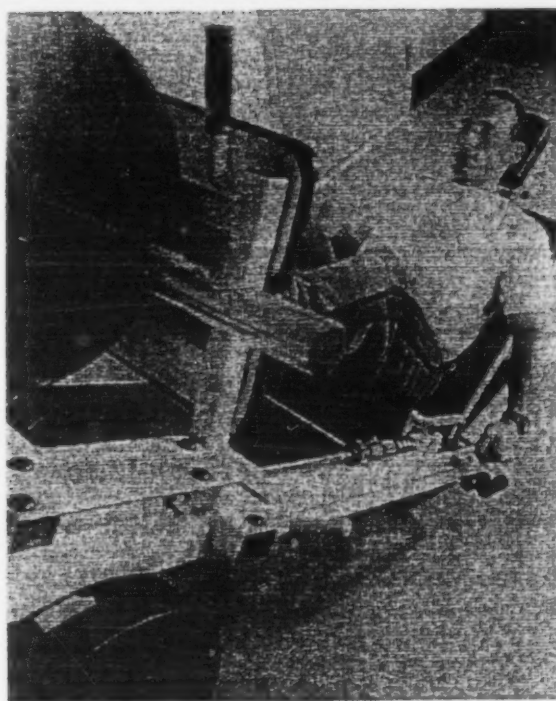


FIGURE 1—Supine leg-press exercise.

Assessment of 1-RM. Before the subjects began their assessment, they were placed in the proper lifting position and executed a movement throughout the complete range of motion for each exercise. The range of motion for the bench press consisted of lowering the bar from full elbow extension to the chest and then returning to full elbow extension. Range of motion on the leg press started at 90° angle knee flexion followed by full knee extension.

After a light warm-up of 10 repetitions at one-third body weight for bench press and an amount equal to the subject's body weight for leg press, the determination of 10-RM began. A trial and error method was used. If an attempt was made with ease, 25% more weight for bench press or 50% more weight for leg press was added to the resistance. Repetitions were done to failure maintaining a steady cadence as long as possible, i.e., no pause at the end of each rep. Once the subject performed a set with the weight that they could lift no more than 10 times, the weight used and the number of repetitions performed were extrapolated to a 1-RM (27). Using the predicted data for the subjects 1-RM test, 70% and 80% of 1-RM values for the bench and leg press, respectively, were selected as the weight to be used during the supersets (SS). An SS was defined as the completion of a leg set and bench set executed in succession without a rest.

One week after the first visit, the subjects underwent the first of two familiarization trials. They reported to the laboratory in the morning in a fasted but hydrated state. They were given a standardized meal of two food servings and a 557-mL bottle of fruit juice. The food was chosen from

servings of white toast, muffins, or bagels. The juice was apple or orange. Once the food and juice were selected, they were used for all remaining trials. Fifteen minutes after the meal, a 5-mL blood sample was taken. This blood sample was taken during a familiarization trial with the sole purpose of familiarizing the subjects with the venous sampling procedures and thereby reduces the probability of a subject experiencing a vasovagal response during experimentation. After another 15 min in a seated posture, blood pressure was measured in the right arm with a standard mercury sphygmomanometer and stethoscope. This was followed by a warm-up on the leg- and bench-press machines with the resistance for the leg press set at 40% 1-RM and the bench at 35% 1-RM. The warm-up consisted of 10 lifts with each weight starting with the legs first. After a 2-min rest, the subject began the actual SS sessions. This consisted of three SS with each SS consisting of the leg press at 80% 1-RM followed immediately by the bench press at 70% 1-RM and then a 2-min rest before the next SS started. The weight lifted remained the same for each set, and each set of each exercise was performed to voluntary fatigue. Session 3 followed session 2 by 1 wk, and it was also a familiarization trial. The subjects were instructed to perform the exercise using a constant cadence and full range of motion. The lift was controlled by placing rubber bands against the bottom of the tracks upon which the weight stack slides, and the subjects were told to lower the weights until the segments were touched by the weight stack and then to immediately begin the concentric phase of the lift.

Sessions 4–8 consisted of the treatment trials (three 4- and two placebo). These trials were identical to the familiarization sessions except for the timing of the ingestion of the treatment and the drawing of the blood sample. Upon arriving at the laboratory, the drug or placebo was immediately ingested. Fifteen minutes later the light meal was consumed. Thirty minutes after drug ingestion, the subjects changed into exercise clothing, and the venous catheter was inserted well in advance of the sampling time so that anxiety about a needle stick would not confound the blood pressure

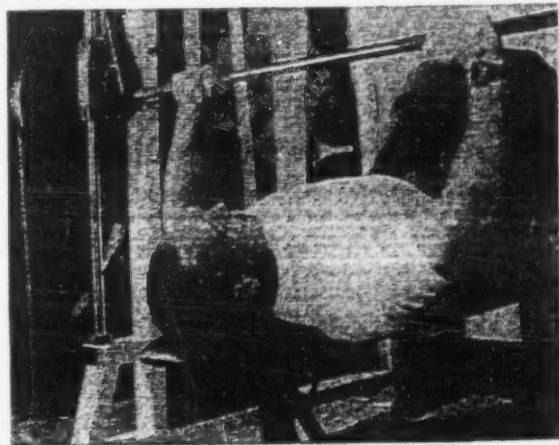


FIGURE 2—Bench-press exercise.

measurement. Blood pressure was measured 85 min after ingesting the trial treatment. A 5-mL blood sample was drawn after the blood pressure reading. The warm-up and SS session commenced 90 min after ingesting the treatment.

Drug and placebo administration. The subjects ingested their drug treatment in gelatin capsules prepared by a technician who was not otherwise involved with the experiments. The treatments were placebo (P), C (4 mg kg⁻¹ body weight of anhydrous caffeine manufactured by Sandoz Canada), E (0.8 mg kg⁻¹ body weight of ephedrine hydrochloride manufactured by Roberts Pharmaceutical Canada), or C+E in combination. The placebo consisted of 300 mg of dietary fiber (Metamucil®) inserted into the same number of capsules as used for the caffeine treatment. This amount of Metamucil® was 100 times less than the recommended dose of the product for its intended use as a dietary laxative. The order of treatments was randomly assigned by the technician who prepared the capsules; she simply verified that the treatment she was about to distribute to a subject had not yet been given to that subject on a preceding trial. Table 1 shows the frequency of the order of treatments.

Measurements. The number of completed repetitions were counted and recorded for each leg- and bench-press set. The total work performed for the bench and leg press was also calculated as the product of the number of repetitions and the weight lifted during the concentric phase of the exercise. Blood was drawn through a Teflon catheter (Desert Medical Inc., Sandy, UT) inserted into an antecubital vein. The catheter was kept patent with a heparin lock (0.25 mL of heparin (10 units mL⁻¹)). Venous blood samples taken just before exercise were immediately expelled into a tube treated with ethylenediamine tetraacetate (EGTA, 90 mg kg⁻¹) and glutathione (60 mg kg⁻¹), then centrifuged at 10°C for 15 min, after which the plasma component was separated and stored at -70°C until assayed for C and E by mass spectrometry (GC-MS) electron-impact, selective-ion monitoring (28).

Data analyses. A 2 × 2 × 3 factorial repeated measures ANOVA was used to determine the effects of caffeine (present or absent) and ephedrine (present or absent) and set (1, 2, or 3) on the number of repetitions performed during each exercise. To generate the placebo values for the above analyses, the mean of the two placebo trials was used. Similar analyses were done on the total work done for bench press, leg press, bench + leg press, and the diastolic and systolic blood pressure measurements. Plasma concentrations of caffeine and ephedrine were analyzed with a one-way repeated measures ANOVA. When a *post hoc* comparison was required, a means comparison contrast technique

was employed, and the Huynh-Feldt-epsilon factors were used to adjust degrees of freedom for multiple comparisons. The results of the two placebo trials were used to evaluate the test-retest reproducibility of the performance test through regression analysis. Statistical significance was accepted at the $P < 0.05$ level.

RESULTS

Caffeine and ephedrine concentrations. There was no difference between the plasma caffeine levels (mean ± SD) 90 min after treatment ingestion and just before exercise when the C (35.3 ± 5.2 μM) and C+E (34.0 ± 5.8 μM) trials were compared. Similarly, there was no difference between the plasma ephedrine levels for the E (1.493 ± 0.283 μM) and C+E (1.466 ± 0.202 μM) trials. No caffeine or ephedrine was detectable in the plasma samples for the placebo trials, which was confirmation that the subjects likely adhered to the request that they avoid caffeine for 2 d before each trial.

Blood pressure. The mean ± SD values for systolic blood pressures measured just before exercise were 137 ± 12, 141 ± 16, 150 ± 14, and 156 ± 29 mm Hg for P, C, E, and C+E, respectively. Analyses showed that the trials involving ephedrine ingestion (mean value for E and E+C was 153 ± 22 mm Hg) caused significant increases in systolic blood pressure compared with the nonephedrine trials (mean value for P and C was 139 ± 14 mm Hg). The treatments did not affect diastolic blood pressure. Diastolic blood pressures were 80 ± 6, 82 ± 6, 82 ± 8, and 85 ± 11 for P, C, E, and C+E, respectively. Two subjects displayed extremely high hypertensive responses to the C+E treatment. The subjects were otherwise normotensive but had preexercise blood pressures of 204/90 and 214/112 ninety minutes after ingesting the C+E treatment. A physician monitoring the study consulted with the subjects, measured blood pressure again 10 min later at which point it had decreased slightly, and then the trial continued under the supervision of the physician. Both subjects displayed elevated systolic blood pressure on all of their trials; their two placebo trial values were 156 and 168 mm Hg for one subject and 130 and 164 mm Hg for the other. Neither subject had a history of hypertension at the time this manuscript was written over a year after the conclusion of the data collection.

Leg- and bench-press performance. Table 2 shows the number of repetitions performed for each set after each treatment for both exercises. There was no significant trial order effect for either the leg- ($P = 0.82$) or bench-press ($P = 0.80$) exercises. The mean number of repetitions for leg press was significantly higher, but only in the first set, for the trials involving ephedrine treatment (C+E = 18.5 ± 8.4, E = 16.3 ± 7.2) when compared with the nonephedrine trials (C = 13.6 ± 6.5; $P = 12.5 ± 5.0$). Similarly for the bench-press exercise, the ephedrine treatments were associated with significantly more repetitions during the first set only (C+E = 14.3 ± 3.1; E = 13.3 ± 2.9) when compared with the nonephedrine treatment trials (C = 12.4 ± 2.7, P

TABLE 1 The frequency of treatments on each sequential treatment trial

Treatment Trial Order	No. of Subjects Treated with				
	Caffeine	Ephedrine	C+E	Placebo 1	Placebo 2
First	2	3	3	5	0
Second	2	3	3	3	2
Third	3	3	2	4	1
Fourth	3	3	2	1	4
Fifth	2	2	3	0	6

TABLE 2 Number of repetitions (mean $\pm$ SD, $N = 13$) completed during leg- and bench-press sets after caffeine (C), ephedrine (E), C+E, or placebo (P) ingestion

	Placebo	Caffeine	Ephedrine	C+E
Leg Press				
Set 1*	12.5 $\pm$ 5.0	13.6 $\pm$ 6.5	16.3 $\pm$ 7.2*	18.5 $\pm$ 8.4*
Set 2	9.1 $\pm$ 5.1	9.1 $\pm$ 5.7	9.6 $\pm$ 4.1	10.4 $\pm$ 5.8
Set 3	7.2 $\pm$ 3.8	6.5 $\pm$ 4.5	7.0 $\pm$ 3.8	7.5 $\pm$ 4.8
Bench Press				
Set 1*	12.3 $\pm$ 2.9	12.4 $\pm$ 2.7	13.3 $\pm$ 2.9*	14.3 $\pm$ 3.1*
Set 2	8.2 $\pm$ 2.0	8.1 $\pm$ 2.1	7.9 $\pm$ 1.9	8.4 $\pm$ 2.5
Set 3	5.8 $\pm$ 1.7	4.9 $\pm$ 1.8	4.6 $\pm$ 2.1	4.5 $\pm$ 1.9

* Ephedrine trials (E and C+E) > nonephedrine trials (P and C)

* Set 1 > set 2 > set 3

= 12.3 $\pm$ 2.9). The E and the C+E trials were not different. There was no significant interaction of the drug treatments.

As expected, the number of repetitions decreased with each successive set. The total work performed during the three SS was similar when individual treatment trials were compared with the one-way repeated measures ANOVA. The factorial ANOVA, however, indicated that the total work performed for the leg press and the combination of leg and bench press was significantly increased after ephedrine ingestion, i.e., the ephedrine trials (E and C+E) were significantly greater than the nonephedrine trials (P and C) (Table 3).

The results from the two placebo trials were used to evaluate the reproducibility of the test procedures through regression analysis. When the individual sets of a given exercise were compared, e.g., first set of first P trial compared with the first set of the second P trial, etc., the number of repetitions completed within each set were highly correlated with coefficients ranging from 0.80 to 0.98 for the leg-press exercise but lower for the bench press where the coefficients ranged from 0.70 to 0.78. All regression coefficients were significant for both types of exercise. Figs 3 and 4 show the test-retest reproducibility by displaying the pooled data from all of the sets for both the first and second placebo treatment trials (i.e., the first set of the first placebo trial are plotted against the first set of the second placebo trial, the second set of the first placebo trial are plotted against the second set of the second placebo trial, etc.). The regression coefficients for both types of exercise were very high, 0.81 for the leg press and 0.91 for the bench-press exercise. For both types of exercise, the regression analysis indicated that the intercept of the regression was both positive and significantly different from zero.

DISCUSSION

In the present study, it was hypothesized that the C+E treatment would improve muscular endurance and that the

TABLE 3 Total work (mean $\pm$ SD, $N = 13$) performed during leg- and bench-press sets after caffeine (C), ephedrine (E), C+E, or placebo (P) ingestion. Work was calculated as the product of the number of repetitions and the weight lifted during the concentric phase of the exercise

	Placebo	Caffeine	Ephedrine	C+E
Leg (kg)	6664 $\pm$ 2654	5825 $\pm$ 3120	7798 $\pm$ 3316*	8265 $\pm$ 3634*
Bench (kg)	1683 $\pm$ 534	1621 $\pm$ 509	1643 $\pm$ 517	1724 $\pm$ 484
Leg + bench (kg)	8347 $\pm$ 2724	7546 $\pm$ 2971	9442 $\pm$ 3306*	9989 $\pm$ 3586*

* Ephedrine trials (E and C+E) > nonephedrine trials (P and C)

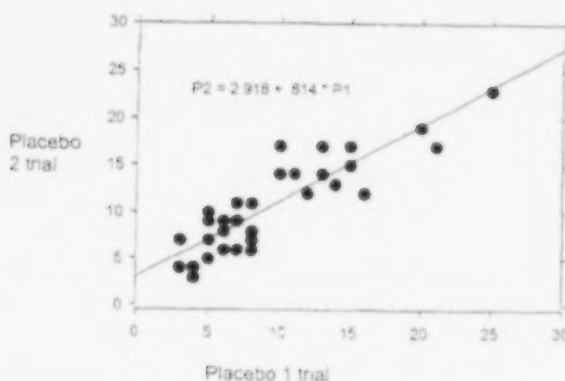


FIGURE 3—Performance reproducibility for leg-press exercise. The number of repetitions completed during each set of leg-press exercise during the first placebo trial is regressed against the data from the second trial.

magnitude of the improvement would be greater than improvements that might be caused by ingesting either C or E alone. The results support the first part of the hypothesis, i.e., C+E did markedly improve performance during resistance training type exercise, albeit transiently because it was only exhibited during the first set of exercise. The magnitude of the effect during that first set is highly significant for this type of exercise, considering that it was induced only 90 min after ingesting the C+E. The 48% improvement in the leg exercise and the 16% improvement in bench-press performance would otherwise be expected to require from 4 to approximately 12 wk of strength training, depending on the initial training status of the subjects (2,24). These results, however, should be considered in light of the evidence suggesting a learning effect throughout the experiment. Although there was no "order" effect of trials, the analysis of the two placebo trials indicated that the second P trial was systematically higher than the first placebo trial. Other than the second placebo trial always occurring after the first, the order of the remainder of the treatment trials was randomized, as is shown in Table 1; thus, we are confident that the ANOVA results still strongly support the conclusion that there was an ergogenic effect of the C+E ingestion on this type of exercise.

The hypothesis was not supported entirely, however, because there was no evidence of an additive or synergistic interaction between the C and E. This finding contrasts with earlier research into the effects of C+E on cycle ergometer exercise time to exhaustion at 80% maximal aerobic power (9) where the C and E did appear to interact additively (10). Thus, in the current study ephedrine ingestion, either alone or together with caffeine, was associated with a significant improvement in the number of repetitions that could be performed until exhaustion. Presuming that the treatment effects are likely related to the blood concentrations of C and E when exercise commenced, then these results are consistent with the observation that the C and E blood concentrations were similar regardless of whether the C and E were ingested alone or in combination.

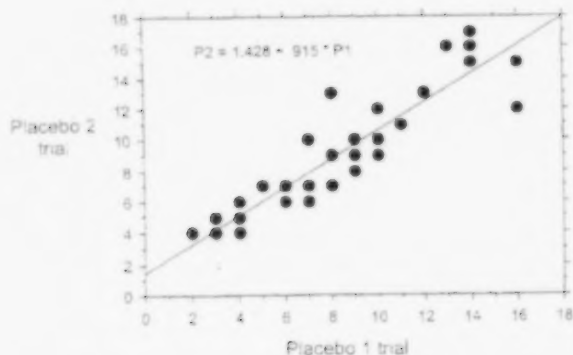


FIGURE 4—Performance reproducibility for bench-press exercise. The number of repetitions completed during each set of bench-press exercise during the first placebo trial is regressed against the data from the second trial.

Both lower- and upper-body performance were affected with ephedrine ingestion, but the increase was more dramatic for the leg-press exercise. If the performance enhancement is related to CNS stimulation, then associated effects could include the release of inhibitory mechanisms leading to increased motor unit recruitment and/or masking of fatigue. Such effects are consistent with the observation by Kalmar and Cafarelli (21) that the level of muscle activation during a maximal voluntary isometric contraction is increased after caffeine ingestion. Therefore, it could be expected that a greater improvement would occur where more innervation has the potential to be affected, such as when a larger muscle mass is recruited. This would explain the greater effect for the leg press.

The observation that the improvement occurred only in the first set may be related to the short rest interval between the SS. It is well established that prior exercise can impair subsequent exercise performance in a manner that is directly related to the intensity of the prior exercise (20,22,23) and the duration of the intervening recovery period (1). Thus, it is tempting to speculate that a more prolonged recovery interval between the SS may have facilitated a continuing ergogenic effect of the ephedrine treatments in subsequent sets.

The results of the current study add to a slowly growing body of literature about the effects of ephedrine ingestion, either alone or in combination with caffeine, on exercise performance. The intensities of exercise examined include relatively high-intensity aerobic exercise leading to exhaustion within 12 to about 45 min (6,8,9,12), supramaximal intensity exercise that challenges both the capacity and the rate at which energy can be transduced via anaerobic metabolism (7), and, with this study, muscular endurance during isomertal weight-lifting exercise. Given the broad range of intensities affected, it is likely that the effects of the drugs are both local and central in nature. In the current study, however, the duration and intensity of the exercise performance make it unlikely that the observed ergogenic effects were due primarily to local effects on the rate of skeletal muscle energy metabolism. A more plausible explanation is

that the increase in muscular endurance with C+E was mediated by an increase in CNS stimulation, which may have delayed or masked the perception of fatigue. Such an explanation is consistent with previous reports that subject RPE were significantly reduced during cycle ergometry at the same absolute exercise intensity after C+E ingestion (8). Similarly, the RPE were significantly lower at the same running pace after C+E (12).

We did not ask the subjects to rate their perceived exertion in the current investigation. Our experience during pilot experiments for this study was that RPE is not a sensitive dependent variable during such exertion if a rating is recorded at the point of fatigue (i.e., when another rep cannot be completed) because virtually everyone picks the maximum rating. It would be useful in future investigations, however, to ask for a RPE after a specific number of reps, e.g., the fifth rep, on each treatment for purposes of comparing the treatments.

Although blood measurements in the current study were limited to analysis of caffeine and ephedrine concentrations after treatment, the effects of similar doses of C and E on a variety of blood metabolites and catecholamines have been summarized elsewhere (7). Significantly higher levels of resting catecholamines, glucose, and lactate before exercise were observed, suggesting that C+E has an effect akin to "priming" of a variety of physiological systems for intense exertion. In terms of CNS arousal, the increased stimulatory effect likely occurs in the brainstem area where C and E would act to modulate specific G-protein-coupled receptors (i.e., adenosine, α and β adrenergic receptors) in the noradrenergic, dopaminergic, serotonergic, and cholinergic systems as well as affecting adenosine receptors in the vascular and neural tissues of the brain (15,16,26). The resultant cascade of cellular events that follow adenosine receptor blockade, including increased dopamine and noradrenaline release (16), has been proposed as key regulatory mechanisms to explain the ergogenic effect of the drug.

All of the subjects in this study were regular consumers of caffeine-containing foods and beverages. Their normal dietary intake of caffeine was not investigated in this study, but it is certainly conceivable that individuals can ingest daily in their diet an amount of caffeine that is similar to the acute dose ingested in this investigation (16). The question of sensitivity to caffeine is therefore raised. It was reported in a recent publication by Bell and McLellan (11) that the ergogenic effect of caffeine ingestion was more pronounced and long lasting in subjects who were nonusers of caffeine when compared with regular users. They speculated that the differences could be attributed to a reported up-regulation in the number of adenosine receptors in the neural and vascular tissues of the brain in caffeine users (16) and that such up-regulation would mean that nonusers would likely be more sensitive to the adenosine antagonistic effects of caffeine. Although the dose of caffeine was slightly larger in their study (5 vs our 4 mg kg^{-1}), it would be interesting to clarify in another investigation whether their findings extend to performance such as that employed in the current investigation.

Ephedrine treatments in the current study involved ingestion of 0.8 mg kg⁻¹. Contrasting with dietary caffeine habits, we found no literature addressing the issue of adaptation to chronic ephedrine ingestion at levels similar to this dose. There is, however, indirect evidence from Toubro et al. (26), who studied weight-loss interventions in a sample of 180 obese patients. They compared the effects of diet and either an ephedrine/caffeine combination (20 mg/200 mg), ephedrine (20 mg), caffeine (200 mg), or placebo 3 × d⁻¹ for 24 wk. Their C+E combination was an effective weight loss treatment, and there was no suggestion in their study that chronic ingestion of ephedrine affected sensitivity to the effects of ephedrine over a period of months. We could find no information, however, that provides insight into the likely response to acute ephedrine treatment, or C+E treatment, in subjects who have ingested ephedrine chronically.

Care was taken to question the subjects in the current investigation to verify that none of them was ingesting caffeine (other than normal nutritional caffeine) or ephedrine supplements or related precursors and analogs. Some caution should be used, however, in evaluating the results because of the lack of clarification of additional nutritional supplements that may have been ingested by the subjects and their potential for interaction with the drug treatments. Such an experimental control should be employed in future related research.

Our research should not be construed as advocacy for athletes or recreational fitness enthusiasts to use ephedrine or other ephedra alkaloid-containing (EAC) products. We acknowledge that there are serious risks such as that dem-

onstrated by the hypertensive responses observed in subjects in this study. However, the fact remains that huge numbers of consumers are estimated to be purchasing and ingesting EAC products, specifically with a view to enhancing physical performance. This study provides some empirical evidence about the efficacy of C+E and, taken together with the related research, will perhaps lead to a greater understanding as to why such products are used, in spite of the potential health risks. It should be noted, however, that there is little, if any, scientific evidence that documents the associated health risks of acute or chronic use of C+E in prospectively designed studies. It is our hope that this research will stimulate others to generate a valid empirical base for such evaluations.

It is important to note that the drugs used in the current investigation were USP-grade ephedrine hydrochloride and anhydrous caffeine. Without conducting controlled studies, it would be inappropriate to infer that similar results would be obtained with other forms of ephedrine or ephedra analogs. For example, in studies where much lower and less potent doses of pseudoephedrine have been used, no ergogenic effects were reported (14,17,25).

In conclusion, ephedrine ingestion, either alone or in combination with caffeine, led to a significant increase in the number of repetitions that could be performed and the total amount of weight that could be lifted during weight training exercise. The increase was observed 90 min after ingesting the ephedrine, and the magnitude of the increased performance is one that normally requires several weeks of strength training.

REFERENCES

1. ABDESSEMED, D., P. DUCHE, C. HAUTIER, G. POUMARAT, and M. BEDU. Effect of recovery duration on muscular power and blood lactate during the bench press exercise. *Int J Sports Med* 20: 368-373, 1999.
2. ALLEN, T. E., R. J. BYRD, and D. P. SMITH. Hemodynamic consequences of circuit weight training. *Res Q* 47:299-307, 1976.
3. ASTRUP, A., L. BAEUM, and S. TOUBRO. Pharmacological and clinical studies of ephedrine and other thermogenic agonists. *Obes Res* 3(Suppl. 4):537S-540S, 1995.
4. ASTRUP, A., S. TOUBRO, S. CANNON, P. HEIN, and J. MADSEN. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study. *Metabolism* 40:323-329, 1991.
5. ATKINSON, R. L., R. C. BLANK, J. F. LOPER, D. SCHUMACHER, and R. A. LUTES. Combined drug treatment of obesity. *Obes Res* 3(Suppl. 4):497S-500S, 1995.
6. BELL, D. G., and I. JACOBS. Combined caffeine and ephedrine ingestion improves run times of Canadian Forces Warrior Test. *Aviat Space Environ Med* 70:325-329, 1999.
7. BELL, D. G., I. JACOBS, and K. ELLERINGTON. Caffeine and ephedrine ingestion effect on anaerobic exercise performance. *Med Sci Sports Exerc* 33:1399-1403, 2001.
8. BELL, D. G., I. JACOBS, T. M. MCLELLAN, and J. ZAMECHNIK. Reducing the dose of combined caffeine and ephedrine preserves the ergogenic effect. *Aviat Space Environ Med* 71:415-419, 2000.
9. BELL, D. G., I. JACOBS, and J. ZAMECHNIK. Effects of caffeine, ephedrine and their combination on time to exhaustion during high-intensity exercise. *Eur J Appl Physiol Occup Physiol* 77:427-433, 1998.
10. BELL, D. G., I. JACOBS, and J. ZAMECHNIK. Reply to Morton letter. *Eur J Appl Physiol* 80:611-612, 1999.
11. BELL, D. G., and T. MCLELLAN. Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. *J Appl Physiol* 93:1227-1234, 2002.
12. BELL, D. G., T. M. MCLELLAN, and C. M. SABISTON. Effect of ingesting caffeine and ephedrine on 10-km run performance. *Med Sci Sports Exerc* 34:344-349, 2002.
13. BOOZER, C. N., P. A. DALY, P. HOMEL, et al. Herbal ephedra/caffeine for weight loss: a 6 month randomized safety and efficacy trial. *Int J Obes Relat Metab Disord* 26:593-604, 2002.
14. CLEMENS, J. M., and S. L. CROSBY. Cardiopulmonary and subjective effects of a 60 mg dose of pseudoephedrine on graded treadmill exercise. *J Sports Med Phys Fitness* 33:405-412, 1993.
15. DULLOO, A. G., J. SEYDOUX, and L. GIRARDIER. Peripheral mechanisms of thermogenesis induced by ephedrine and caffeine in brown adipose tissue. *Int J Obes* 15:317-326, 1991.
16. FREDHOLM, B. B., K. BATTIG, J. HOLMEN, A. NEHLIG, and E. E. ZVARTAU. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol. Rev.* 51:83-133, 1999.
17. GILLIES, H., W. E. DERMAN, T. D. NOAKES, P. SMITH, A. EVANS, and G. GABRIELS. Pseudoephedrine is without ergogenic effects during prolonged exercise. *J Appl Physiol* 81:2611-2617, 1996.
18. HALLER, C. K., and N. L. BENOWITZ. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 343:1833-1838, 2000.
19. HUTCHINS, G. M., S. TRAUB, S. HOYEK, et al. Dietary supplements containing ephedra alkaloids. *N Engl J Med* 344:1095-1097, 2001.

20. JACOBS, I., A. J. HERMISTON, and J. D. SYMONS. Effects of prior exercise or ammonium chloride ingestion on muscular strength and endurance. *Med Sci Sports Exerc* 25:809-814, 1993.
21. KALMAR, J. M., and E. CAFARELLI. Effects of caffeine on neuromuscular function. *J Appl Physiol* 87:801-808, 1999.
22. KARLSSON, J., F. BONDE-PETERSEN, J. HENRIKSSON, and H. G. KNUTTGEN. Effects of previous exercise with arms or legs on metabolism and performance in exhaustive exercise. *J Appl Physiol* 38:763-767, 1975.
23. KLAUSEN, K., H. G. KNUTTGEN, and H. V. FORESTER. Effect of preexisting high blood lactate concentration on maximal exercise performance. *Scand J Clin Lab Invest* 30:415-419, 1972.
24. SALE, D. G., I. JACOBS, J. D. MACDOUGALL, and S. GARNER. Interaction between concurrent strength and endurance training. *J Appl Physiol* 68:260-270, 1990.
25. SENEY, K. H., and N. M. LEFEB. The effects of ephedrine on the physiological and psychological responses to submaximal and maximal exercise in man. *Med Sci Sports* 9:95-99, 1977.
26. TOUBRO, S., A. V. ASTRUP, L. BREUM, and F. QUADE. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. *Int J Obes. Relat Metab Disord* 17(Suppl 1):S69-S72, 1993.
27. WERNER, W. K. Relationship between repetitions and selected percentages of one repetition maximum. *J Appl Sport Sci. Res* 1:11-13, 1987.
28. ZAMECHNIK, J. Quantification of epinephrine, norepinephrine, dopamine, metanephrine, and normetanephrine in human plasma using negative ion chemical ionization GC-MS. *Can J Anal Sci Spectroscopy* 42:106-112, 1997.

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